Listening to fluoxetine: a hot message from the FLAME trial of poststroke motor recovery

Steven C. Cramer*

The fluoxetine for motor recovery after acute ischemic stroke study was a double blind, placebo-controlled trial examining the effects of fluoxetine in patients five- to 10 days after an ischemic stroke. The study found motor improvement to 90 days poststroke, measured as the change in the Fugl–Meyer score, was significantly greater in the fluoxetine group as compared with the placebo group, and that this finding was significant after adjusting for depression. Patients randomized to fluoxetine also had less disability (modified Rankin Scale 0–2). The study adds to the weight of data suggesting that viable strategies exist to improve patient outcomes by initiating a restorative agent, days after stroke injury is fixed. Stroke remains among the leading causes of human disability. Currently, a minority of patients can access approved reperfusion therapies, and among those so treated a substantial fraction derives limited benefit. Therapies that target restorative events have a time window measured in days–weeks and so hold the potential to help many patients with stroke.

Key words: clinical trial, plasticity, recovery, selective serotonin reuptake inhibitors, stroke

Numerous approaches are being pursued for promoting brain repair after stroke (1). Growth factors, monoclonal antibodies, cells, electromagnetic brain stimulation, lasers, robotic devices, intensive physiotherapy regimens, and small molecules have each been examined, and are at various stages of development. The category of small molecules is particularly broad and includes modulation of brain neurotransmitters. Although much of the focus on neurotransmitters to date has been on drugs affecting catecholamines, recent studies also support therapies targeting serotonin.

Serotonin is a monoamine neurotransmitter that is central to numerous brain functions, particularly affect and cognition, and can influence motor cortex activity. Early studies examining selective serotonin reuptake inhibitor (SSRI) effects on poststroke outcomes were favorable, for example, Miyai and Reding (2) found that the reduction in disability provided by fluoxetine for patients in the early weeks after stroke was significantly better than that provided by the noradrenergic drug desipramine or placebo; comparable results were found by Dam *et al.* (3). Pariente *et al.* (4), using functional magnetic resonance imaging in eight subjects two-weeks after a lacunar stroke, found that a single dose of fluoxetine increased ipsilesional motor cortex activity in association with improved function of the affected hand. Recent, larger trials have strengthened the case for SSRI drugs in stroke recovery (5, 6), for example, Jorge *et al.* (6) found that, among 129 patients randomized within three-months of stroke, cognitive outcomes at 12-month poststroke were significantly better among those randomized to the SSRI escitalopram, as compared with problem-solving therapy or placebo. Importantly, these effects were independent of any depression.

It is with this crescendo of SSRI momentum that Chollet *et al.* (7)published the fluoxetine for motor recovery after acute ischemic stroke (FLAME) study. This was a double-blind, placebo-controlled trial that enrolled patients from nine stroke centers in France. Entry criteria included ischemic stroke five- to 10 days old, moderate–severe weakness, age 18–85, NIHSS score $\leq$20, and no depression. Patients were randomized to 20 mg fluoxetine or placebo, orally, once daily, for three-months.

The patients began therapy, at an average of nine-days after a stroke, which was on an average of moderate severity (baseline NIHSS = 13) but with severe weakness. Strokes were predominantly supratentorial nonlacunar infarcts. The rate of IV thrombolysis was high (32%). The primary outcome measure was the change between enrollment and day 90 in the Fugl–Meyer Motor Scale, an assessment of arm and leg motor function with scores ranging from 0 (worst) to 100 (normal). The two groups were well balanced at baseline, though a slight imbalance in motor status favored the fluoxetine group. All enrollees underwent standard physiotherapy concomitant with study medication.

The main finding of the study was that the change in Fugl–Meyer score in the fluoxetine group was significantly greater than in the placebo group (34 vs. 24 points, $P = 0.003$). This gain remained significant after adjustment for depression

Correspondence: Steven C. Cramer*, UC Irvine Medical Center, 101 The City Drive South, Building 53 Room 203, Orange, CA 92868-4280, USA.
E-mail: scramer@uci.edu
Departments of Neurology, Anatomy & Neurobiology, University of California, Irvine, CA, USA

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diagnosis, and was apparent in both affected arm and leg. Regarding global outcome measures, responder analysis showed a significant effect for the modified Rankin Scale (% patients with 0–2) but not for the NIHSS (% patients with 0–5). Depression was four times more common among patients in the placebo group.

The FLAME study is small by some standards and so independent replication will be welcomed. Remarkably, primary analysis included some patients in the placebo arm who developed depression and were switched to open label fluoxetine. This indicates that the true difference between fluoxetine and placebo might be greater than current results suggested.

The FLAME study raise issues central to restorative stroke trials (8). First, the results lend support to modality-specific endpoints in restorative stroke trials. The Fugl–Meyer score demonstrated a significant difference in motor gains between the two treatment arms, whereas only some of the global endpoints did. In a restorative trial setting, some neurological domains such as motor or language might improve while others, such as those whose anatomical underpinnings are decimated by stroke, might not. Restorative trials might therefore include modality-specific endpoints to best capture treatment effects, and also include appropriate measures of activity and participation to best interpret these effects (9). Second, stroke recovery occurs on the backbone of neural plasticity events that are experience-dependent (10). Physiotherapy, speech therapy, and other experiences provided in parallel to restorative drug exposure are thus part of the equation. Further studies are needed in this area, for example, to understand how specific dimensions of concomitant experience influence drug effects, or how to best capture the extent of these therapies.

Exciting results generate many questions. How will the FLAME results extend to stroke populations with a broader range of baseline deficits? What is the therapeutic time window for initiating therapy, e.g. can we help patients with fixed deficits five-years poststroke? Do the findings persist at one-year poststroke? In this regard, do the gains provided by 90 days of fluoxetine stay or go if the drug is discontinued? Can those patients most likely to respond to this restorative agent be prospectively identified?

Some clinicians will interpret the FLAME study results as establishing utility of fluoxetine for many patients with motor deficits after stroke, while others will await clarification and replication. Regardless, the FLAME study adds to the weight of data suggesting that viable strategies exist to improve patient outcomes by initiating a restorative agent days after stroke injury is fixed. Chollet *et al.* (7) are to be congratulated for a study that is likely to have a major impact on treating stroke for years to come.

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